DECLE96.001APC

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	:	Reimann, et al.
Appl. No.	:	10/509,498
Filed	:	September 28, 2004
For	:	COMBINED DNA/PROTEIN VACCINE COMPOSITIONS
Examiner	:	unknown
Group Art Unit	:	unknown

CERTIFICATE OF MAILING

I hereby certify that this correspondence and all marked attachments are being deposited with the United States Postal Service as first-class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on

November 29, 2004
(Date)

Che Swyden Chereskin, Reg. No. 41,466

LETTER WITH INTERNATIONAL PRELIMINARY EXAMINATION REPORT

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Enclosed please find the International Preliminary Examination Report issued by the European Patent Office for the International application.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: Nov. 29, 2004

By:
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PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

DE CLERCQ, BRANTS & PARTNERS
E. Gevaertdreef 10a
B-9830 Sint-Martens-Latem
BELGIQUE

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing *(day/month/year)*	13.10.2004
Applicant's or agent's file reference	**IMPORTANT NOTIFICATION**
03/084 PCT	

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP 03/03353	28.03.2003	28.03.2002

Applicant
BRENNTAG BIOSECTOR A/S

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international preliminary examining authority:	Authorized Officer
European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	de Haas, B Tel. +31 70 340-4738

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
03/084 PCT		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP 03/03353	28.03.2003	28.03.2002
International Patent Classification (IPC) or both national classification and IPC		
A61K39/00		
Applicant		
BRENNTAG BIOSECTOR A/S		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 2 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
28.10.2003	13.10.2004
Name and mailing address of the international preliminary examining authority:	Authorized Officer
European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Nooij, F Telephone No. +31 70 340-3267

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/03353

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-13 as originally filed

Claims, Numbers

1-9 received on 19.07.2004 with letter of 19.07.2004

Drawings, Sheets

1/1 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-9
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-9
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-9
	No:	Claims	

2. Citations and explanations

   see separate sheet

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

CITED DOCUMENTS

The following documents are referred to in this communication:

D1: WO 99 30733 A (SMITHKLINE BEECHAM BIOLOGICALS S.A.) 24 June 1999 (1999-06-24)
D2: WO 00 02591 A (MERCK & CO, INC.) 20 January 2000 (2000-01-20)
D3: WO 97 28818 A (THEREXSYS LIMITED) 14 Augustus 1997 (1997-08-14)

1. ADDED SUBJECT-MATTER (Article 34(2)(b) PCT)

1.1 The amendments filed with the letter dated 19.07.2004 does not introduce subject-matter which extends beyond the content of the application as filed, and complies with Article 34(2)(b) PCT.

2. NOVELTY (Article 33(2) PCT)

2.1. *D1* discloses simultaneous vaccination with DNA and protein. May be adjuvanted with aluminium phosphate (see page 9, lines 18-27, and the claims).

2.2 *D2* discloses a vaccine composition comprising (a) a polynucleotide vaccine component, e.g. encoding HBsAg or influenza virus, and (b) a mineral-based adjuvant, e.g. aluminium or calcium phosphate. Said vaccine composition may additionally include antigenic protein (see page 20, lines 21-27).

2.3 *D3* discloses a combination (mixture or complex) for vaccination, comprising a nucleic acid encoding a first epitope and a peptide containing a second epitope. May be combined with an adjuvant, e.g. aluminium phosphate.

2.4 None of the cited documents *D1-D3* disclose that the mineral-based negatively charged adjuvant is preincubated or subsequently mixed with said at least protein antigen vaccine prior to being formulated with said polynucleotide vaccine

component.

2.5 In view of the prior art cited, present (new) claim **1** as well as present claims **2-9** appear to be novel and meet therefore the requirements of Article 33(2) PCT.

2.6 Although new claim **1** relates to a vaccine composition characterized by a method, said composition meets the requirements of the PCT, since the applicant has demonstrated, e.g. on page page 6, line 10-22 and in the examples, that the technical differences between the new claimed process used to define the composition in the application, as in present (new) claim **9**, and the process of the state of the art result in a different composition.

3. INVENTIVE STEP (Article 33(3) PCT)

3.1. With regard to present claim **1**, *D1* is considered to represent the most relevant state of the art and discloses the simultaneous vaccination with DNA and protein. This mixture or complex may be adjuvanted with aluminium phosphate (see page 9, lines 18-27, and the claims).

3.2 The subject-matter of present claim **1** differs in that the mineral-based negatively charged adjuvant is preincubated or subsequently mixed with said at least protein antigen vaccine prior to being formulated with said polynucleotide vaccine component.

3.3 The problem to be solved by the present invention may therefore be regarded as providing a vaccine composition in which the mineral-based negatively-charged adjuvant-mediated enhancement of the immunogenicity of DNA vaccines is further improved.

3.4 The proposed solution is a vaccine composition wherein the mineral-based negatively-charged adjuvant is preincubated or subsequently mixed with at least one protein antigen vaccine component prior to being formulated with the polynucleotide vaccine component.

3.5 This solution has not been disclosed, nor suggested, in the prior art, and, hence, the subject-matter of present claim **1** and the present dependent claims **2-6** involves an inventive step in the sense of Article 33(3) PCT.

3.6 The same reasoning applies to present independent claims **7-9**, since their subject-matter refers back to the vaccine composition of claims **1-6**.

3.7. In view of the above, the subject matter of present claims **1-9** involves an inventive step and therefore fulfills the requirements of Article 33(3) PCT.

4. FURTHER REMARKS

4.1 The term 'subsequently' in present (new) claim **1** is vague and unclear and leaves the reader in doubt as to the meaning of the technical features to which it refers, thereby rendering the definition of the subject-matter of said claim unclear in the sense of Article 6 PCT.

4.2 Since the combined DNA/protein-based vaccine composition of present claim **1** already includes the use of a mineral-based, negatively charged adjuvant as a component, the subject-matter of present claim **8** is merely a repetition and therefore does not fulfill the requirements of Article 6 PCT with regard to conciseness.

4.3 Present (new) claim **9** refers to a method for preparing a vaccine composition according to a.o. present (new) claim **1**, the latter which has also been characterized by the same method. Present claim **9** is therefore unclear in the sense of Article 6 PCT.

Claims (retyped)

1. A vaccine composition suitable for administration to a vertebrate host, including man, which comprises:

(a) a polynucleotide vaccine component comprising at least one polynucleotide encoding at least one antigen, such that introduction of said formulation into said vertebrate host results in expression of a biologically effective amount of said antigen or antigens so as to induce a prophylactic or therapeutic immune response;

(b) a protein antigen vaccine component comprising at least one protein antigen selected from the group of model protein antigens and vaccine protein antigens; and

(c) a mineral-based, negatively charged adjuvant,

further characterized in that said mineral-based, negatively charged adjuvant is prepared by preincubating or subsequently mixing with said at least one protein antigen vaccine component prior to formulating with said polynucleotide vaccine component.

2. A vaccine composition according to claim 1, wherein said mineral-based negatively charged adjuvant is an aluminium salt or a calcium salt.

3. A vaccine composition according to claim 2, wherein said aluminium or calcium salt is selected from the group consisting of aluminium phosphate, aluminium hydroxyphosphate, phosphate-treated aluminium hydroxide, calcium phosphate, calcium hydroxyphosphate, and phosphate-treated calcium hydroxide.

4. A vaccine composition according to any one of claims 1 to 3, wherein said group of model protein antigens range from acidic IEP proteins to alkaline IEP proteins.

5. A vaccine composition according to any one of claims 1 to 4, wherein said group of vaccine protein antigens includes a surface protein or a core protein of HBV, a de-toxified toxin from the bacteria Clostridium tetani (i. e. tetanus toxoid), a de-toxified toxin from the bacteria Clostridium botulinus (i. e. botulinus toxoid), and a de-toxified toxin from the bacteria Corynebacterium diphtheriae (i. e. diphtheria toxoid).

6. A vaccine composition according to any one of claims 1 to 4, wherein said group of vaccine protein antigens includes protein antigens derived from inactivated poliovirus.

7. A kit comprising a vaccine composition as defined in any one of the claims 1-6 in a unit dose form for administration to a vertebrate recipient, including man.

8. Use of a mineral-based, negatively charged adjuvant as a component in a combined DNA/protein-based vaccine composition as defined in any one of claims 1-6.

9. A method for preparing a vaccine composition according to any of claims 1 to 6, wherein a mineral-based negatively charged adjuvant is preincubated or subsequently mixed with at least one protein antigen vaccine component prior to formulating with a polynucleotide vaccine component.